Cochrane Library

Cochrane Database of Systematic Reviews

Cordyceps sinensis (a traditional Chinese medicine) for kidney transplant recipients (Review)

Hong T, Zhang M, Fan J

Hong T, Zhang M, Fan J.
Cordyceps sinensis (a traditional Chinese medicine) for kidney transplant recipients.
Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD009698.
DOI: 10.1002/14651858.CD009698.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Cordyceps sinensis (a traditional Chinese medicine) for kidney transplant recipients

Tao Hong[1], Minghua Zhang[2], Junming Fan[3]

[1]Department of Nephrology, Sixth People's Hospital of Chengdu, Chengdu, China. [2]Department of Nephrology, The First College of Clinical Medical Science of China Three Gorges University;Yichang Central People's Hospital, Yichang, China. [3]Department of Nephrology, The Affiliated Traditional Chinese Medicine Hospital of Luzhou Medical College, Luzhou City, China

Contact: Junming Fan, Department of Nephrology, The Affiliated Traditional Chinese Medicine Hospital of Luzhou Medical College, Luzhou City, Sichuan Province, 646001, China. junmingfan@163.com, jmfan222@hotmail.com.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 10, 2015.

Citation: Hong T, Zhang M, Fan J. *Cordyceps sinensis* (a traditional Chinese medicine) for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2015, Issue 10. Art. No.: CD009698. DOI: 10.1002/14651858.CD009698.pub2.

ABSTRACT

Background

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease (ESKD). Rising ESKD prevalence has substantially increased numbers of kidney transplants performed. Maintenance immunosuppression is long-term treatment to prevent acute rejection and deterioration of graft function. Although immunosuppressive treatment using drugs such as calcineurin inhibitors (CNIs, such as cyclosporin A (CsA) or tacrolimus) reduce acute rejection rates, long-term allograft survival rates are not significantly enhanced. CNI-related adverse effects contribute to reduced quality of life among kidney transplant recipients. Adjuvant immunosuppressive therapies that could offer a synergetic immunosuppressive effect, while minimising toxicity and reducing side effects, have been explored recently.

Cordyceps sinensis, (Cordyceps) a traditional Chinese medicine, is used as an adjuvant immunosuppressive agent in maintenance treatment for kidney transplantation recipients in China, but there is no consensus about its use as an adjuvant immunosuppressive treatment for kidney transplantation recipients.

Objectives

This review aimed to evaluate the benefits and potential adverse effects of Cordyceps as an adjuvant immunosuppressive treatment for kidney transplant recipients.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register through contact with the Trials Search Co-ordinator to 7 September 2015 using search terms relevant to this review. We also searched Chinese language databases and other resources.

Selection criteria

We included all randomised controlled trials (RCTs) and quasi-RCTs evaluating the benefits and potential side effects of *Cordyceps sinensis* for kidney transplant recipients, irrespective of blinding or publication language. An inclusion criterion was that baseline immunosuppressive therapy must be the same in all study arms.

Data collection and analysis

Two authors extracted data. We derived risk ratios (RR) for dichotomous data and mean differences (MD) for continuous data with 95% confidence intervals (CI).

Main results

Our review included five studies (six reports; 447 participants) that assessed Cordyceps. Limited reporting of study methods and data meant that all included studies were assessed as having unclear risks of bias. The studies investigated Cordyceps compared with azathioprine (AZA) (4 studies, 265 participants) and Cordyceps plus low dose CsA versus standard dose CsA (1 study, 182 participants).

Compared with AZA, Cordyceps showed no significant difference in graft or patient survival, but improved graft function and may reduce acute rejection episodes. Anaemia, leucopenia, and liver function improved, and incidence of infection may also be reduced.

Compared with low dose CsA versus standard dose CsA, Cordyceps did not demonstrate any statistically significant differences in patient survival, graft loss, acute rejection or allograft function. There was limited low quality evidence to suggest benefits in pulmonary infection, serum albumin, serum uric acid levels, CNI nephrotoxicity and hepatotoxicity.

None of the included studies reported on quality of life, and follow-up was short-term (three months to one year). Given the limited number of small studies, and high risk of bias, results should be interpreted with caution.

Authors' conclusions

Although there were some favourable aspects associated with Cordyceps, longer-term studies are needed to clarify any benefit-harm trade-off. Future studies should investigate the use of Cordyceps in combination with other immunosuppressive agents such as tacrolimus, mycophenolate mofetil or induction therapy. Such studies also need to be appropriately sized and powered.

PLAIN LANGUAGE SUMMARY

Cordyceps sinensis (a traditional Chinese medicine) for kidney transplant recipients

Kidney transplant recipients need to take several immunosuppressive drugs following surgery to prevent rejection. However, these drugs can cause side effects which compromise long-term survival for both patients and grafted kidneys.

Cordyceps sinensis (Cordyceps) is used in traditional Chinese medicine settings. Cordyceps is thought to suppress organ rejection, reduce immunosuppressive drug use, and protect patients from drug-related side effects. However, because Cordyceps use is limited beyond settings that routinely treat people using traditional Chinese medicine, its benefits and harms are unclear.

We evaluated the use of Cordyceps following kidney transplantation to assess its safety, benefits and harms. We searched the literature published to September 2015 and found 156 records. Of these, 131 were from Chinese language databases and 25 from non-Chinese language sources. After assessment, we included five studies (six reports) that presented data from 447 adult patients who received Cordyceps treatment following kidney transplantation in China. Overall, we found that reporting and study designs were significantly flawed and may have overestimated benefits and underestimated harms.

Cordyceps was compared with azathioprine (an immunosuppressive drug). We found no significant differences between treatments in terms of patient or kidney survival, or organ rejection. We found some improvement in kidney function, anaemia, leucopenia, liver function and incidence of infection among people who received Cordyceps.

We also analysed Cordyceps in combination with low dose cyclosporin A (CsA, another immunosuppressive drug) versus standard dose CsA. We found no significant differences in patient or kidney survival, organ rejection, or kidney function between treatments. Cordyceps treatment was reported to lead to a reduction in CsA dose, improved rates of lung infection, albumin and uric acid levels in blood. Cordyceps also appeared to offer protective effects against kidney and liver damage that can occur with use of CsA; however this improvement may also have been due to the lower CsA dose.

Our review was limited by the few included studies with small numbers of participants that investigated Cordyceps for kidney transplant recipients. Effects of therapies were observed for very short periods which significantly limited the robustness of reported outcomes. Larger and more robust randomised studies that assess the benefits and harms of Cordyceps for people following kidney transplantation are needed to better inform clinical practice.

BACKGROUND

Description of the condition

Calcineurin inhibitor (CNI)-based immunosuppressive treatment with cyclosporin A (CsA) and tacrolimus can significantly reduce acute rejection rates and provide excellent early outcomes. However, long-term allograft survival rates are not significantly enhanced by these drug therapies (Meier-Kriesche 2004). Chronic allograft injury, a major cause of kidney transplant failure, occurs frequently and often results in requirement for dialysis. Kidney allograft failure is one of the most common causes of end-stage kidney disease (ESKD), and is responsible for 25% to 30% of patients waiting for kidney transplants. In the USA, over 20% of kidney transplant recipients have failed one or more kidney allografts (Vella 2010). In 2013, over 26,000 people In the USA underwent kidney transplantation (OPTN 2015).

CNI nephrotoxicity is a major contributor to chronic allograft injury. Almost all kidney transplant recipients exhibit chronic CsA nephropathy about 10 years after commencement of CNI treatment (Nankivell 2003). CNI use for kidney transplant recipients is also associated with higher prevalence of hypertension and dyslipidaemia and an increased risk of cardiovascular events (de Mattos 2000; Olyaei 2001). CNI-related adverse effects can lead to poor long-term outcomes in kidney transplant recipients. Alternatives to CNI-based adjuvant immunosuppressive therapies that could enhance quality of life and reduce side effects have been explored.

Description of the intervention

Cordyceps sinensis (Cordyceps, Dong Chong Xia Cao), a traditional Chinese medicine, is also known as Chinese caterpillar fungus. It is a complex stroma of a unique parasitic fungus that invades and deposits spores in the larvae of moths. Cordyceps is a traditional tonic herb and has been used recently to treat a wide range of disorders, including kidney, respiratory, liver and cardiovascular diseases in China.

Evidence from animal and in-vitro studies has shown that Cordyceps may be beneficial for kidney transplant recipients. Animal transplant models have reported that Cordyceps can inhibit rejection and prolong allograft survival (Cheng 2006; Luo 2007; Zhang 1990). When combined with CsA, Cordyceps has been reported to exhibit synergistic immunosuppressive effects that can ameliorate CNI nephrotoxicity (Ding 2009a; Zhao 1993). Cordyceps with reduced dose CsA has been shown to suppress rejection as effectively as standard dose CsA alone (Ding 2011; Li 2009). As a replacement for azathioprine (AZA) in immunosuppressive triple therapy, Cordyceps has been reported to confer a similar immunosuppressive effect with fewer side effects compared with conventional therapies (Sun 2004; Yu 1991).

In China, Cordyceps is commonly used as an adjuvant immunosuppressive agent in both initial and long-term maintenance treatment for kidney transplant recipients. Cordyceps is in limited in supply in its natural state but various cultured and fermented mycelial products with similar pharmacologically-active components are now used in clinical practice (Zhu 1998a; Zhu 1998b).

Although Cordyceps has undergone substantial research in recent decades, many therapeutic claims remain unsubstantiated. A specific component responsible for biological activity and the mechanism of its effect has yet to be determined. Almost all published studies of pharmacological actions of Cordyceps were in-vitro or animal models, with few human clinical studies.

There have been no human studies suggesting a dose-response effect with Cordyceps in its natural or artificially cultivated forms, and no comparative studies comparing either form. Although animal studies have suggested that artificially cultivated Cordyceps has limited toxicity in rats and mice (Jian 1995; Jiang 1995; Kong 1995), there have been no human studies investigating the safety of natural or cultivated Cordyceps.

How the intervention might work

It has been suggested that Cordyceps for kidney transplant recipients may:

1. synergistically suppress rejection (Cheng 2006; Ding 2009a; Jordan 2008; Luo 2007; Zhang 1990;Zhao 2007);
2. reduce CNI dose and related side effects (Ding 2009a; Ding 2011; Li 2009);
3. ameliorate CNI nephrotoxicity and improve kidney graft function (Ding 2009a; Xu 1995; Zhao 1993); and
4. decrease prevalence of complications (infections, leucocyte depletion) (Sun 2004; Yu 1991).

Studies on the mechanisms of action of Cordyceps for kidney transplant recipients have suggested that its therapeutic effects may be related to its bidirectional immunomodulating activity (Ka 2006), antioxidant activity (Shin 2001; Yamaguchi 2000), and anti-inflammatory properties (Ding 2009a). Cordyceps may protect grafted kidneys by ameliorating renal tubular impairment and reducing renal interstitial fibrosis (Chai 2009).

Why it is important to do this review

Cordyceps use for kidney transplant recipients is almost exclusively confined to China. Although it has been suggested that Cordyceps may offer benefits for kidney transplant recipients, inherent limitations in study sample size and inappropriate study design means that results cannot be applied with confidence.

Because the safety and efficacy of Cordyceps for kidney transplant recipients had not been systematically appraised, we aimed to assess the therapeutic effect of Cordyceps for kidney transplant recipients and identify areas for improvement in future clinical studies.

OBJECTIVES

This review aimed to evaluate the benefits and potential adverse effects of Cordyceps as an adjuvant immunosuppressive treatment for kidney transplant recipients.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-RCTs (studies in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) evaluating the benefits and potential side

effects of Cordyceps for kidney transplant recipients, irrespective of blinding, publication language, and publication year.

Types of participants

Kidney transplant recipients of any age or sex, with any type of kidney disease causing ESKD were included. Previous kidney graft recipients were also included. Patients who had undergone solid organ transplantation other than kidney (such as kidney and pancreas) were excluded.

Types of interventions

- The interventions eligible to be investigated were Cordyceps or its products as the single treatment drug, regardless of formulation or route of administration. These included extracts of Cordyceps (any part) or any derived, cultured, fermented mycelial products that contain pharmacologically-active components similar to wild Cordyceps. Other Cordyceps species, such as *Cordyceps militaris,* were also included
- Control interventions included placebo, no treatment or conventional treatment
- Co-interventions were permitted where participants in all study arms received the same co-intervention
- Studies of Cordyceps as a component of compounded preparations or as part of a combined treatment regimen were excluded
- Studies that included other herbal or complementary medicines that lack validated efficacy as the control intervention were excluded.

Types of outcome measures

Primary outcomes

1. All-cause mortality
2. Incidence of graft failure (defined as creatinine clearance/glomerular filtration rate (CrCl/GFR) < 15 mL/min or need for dialysis)
3. Incidence of acute rejection (biopsy proven/clinical suspicion)
4. Incidence and degree of chronic allograft injury (biopsy proven/clinical suspicion).

Secondary outcomes

1. Kidney function (measured by GFR, CrCl, or serum creatinine (SCr))
2. Proteinuria (measured by 24 hour urinary protein excretion, protein/creatinine ratio, or albumin/creatinine ratio)
3. Routine urine analysis (urinary erythrocytes, leucocytes and urinary protein (semi quantitative))
4. CNI nephrotoxicity (biopsy proven)
5. CsA (or tacrolimus) dose and whole blood CsA (or tacrolimus) concentration
6. Blood routine examination (haemoglobin (Hb) and white blood cell count)
7. Complications (infection, liver injury, hyperuricaemia)
8. Quality of life (measured by a validated scale)
9. Adverse effects.

Primary and secondary outcome measurements were collected immediately after treatment and at the end of follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register through contact with the Trials' Search Co-ordinator to 7 September 2015 using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from the following sources.

1. Quarterly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney and transplant conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

The following Chinese databases were also searched.

1. CBM (Chinese Biomedical Literature Database) (to 28 February 2014)
2. CNKI (China National Knowledge Infrastructure) (to 28 February 2014)
3. CMAC (China Medical Academic Conferences (to 28 February 2014)
4. TCMLARS (Traditional Chinese Medical Literature Analysis and Retrieval System) (to 28 February 2014)
5. Wanfang Data (to 28 February 2014).

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that could be relevant to the review. The titles and abstracts were screened independently by two authors who discarded studies that were not applicable; however, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and if necessary, the full text of these studies to determine which satisfied the inclusion criteria.

Disagreement was resolved by discussion or arbitration by a third author of review.

Data extraction and management

Data extraction was carried out independently by two authors using a standard data extraction form. Studies reported in non-English or non-Chinese language journals were planned to be translated before assessment. Where more than one publication of one study existed, reports were grouped together and the publication with the most recent complete data was used. Where relevant outcomes were only published in earlier versions these data were used. Any discrepancy between published versions was to be highlighted. Any further information required from the original author was requested by written correspondence and any relevant information obtained in this manner was included in the review. Disagreements between authors were resolved by consultation with a third author.

Assessment of risk of bias in included studies

To detect potential selection bias, performance bias, attrition bias, detection and reporting bias, the following items were assessed using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, incidence of graft failure, acute rejection, chronic allograft injury, CNI nephrotoxicity, complications) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (kidney function, proteinuria, CsA or tacrolimus dose, whole blood CsA or tacrolimus concentration, routine urine examination, blood routine examination, quality of life) the mean difference (MD) with 95% CI were used, or the standardised mean difference (SMD) if different scales had been used.

Dealing with missing data

Whenever possible, we contacted study authors to obtain missing data. Any data obtained in this way were included in the analysis. The potential impact of missing data was considered in the interpretation of the results. For dichotomous outcomes, missing data were investigated by sensitivity analyses of worst-best cases. For continuous outcomes, a fixed difference between the means of missing data and the measured outcome data were assumed in the sensitivity analysis.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.1 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We planned to construct funnel plots to explore bias if more than 10 studies were included in this review (Higgins 2011). However, the small number of included studies (five) meant that this could not be undertaken.

Data synthesis

Data were pooled using the random-effects model but the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to explore potential sources of heterogeneity.

1. Risk of bias (low or unclear)
2. Source (wild or cultivated) and preparation (whole plant or extract) of Cordyceps
3. Use of Cordyceps with or without other treatment (low dose CsA or tacrolimus, standard dose CsA or tacrolimus, AZA)
4. Dose, timing of initiation and/or duration of therapy.

Sensitivity analysis

For dichotomous outcomes, we planned to perform worst-best case analyses to explore the impact of incomplete or missing data. We also planned to conduct sensitivity analyses on adequacy of sequence generation and blinding to explore their influence on effect estimates, but the small number of included studies and inconsistent outcome reporting made this meaningless.

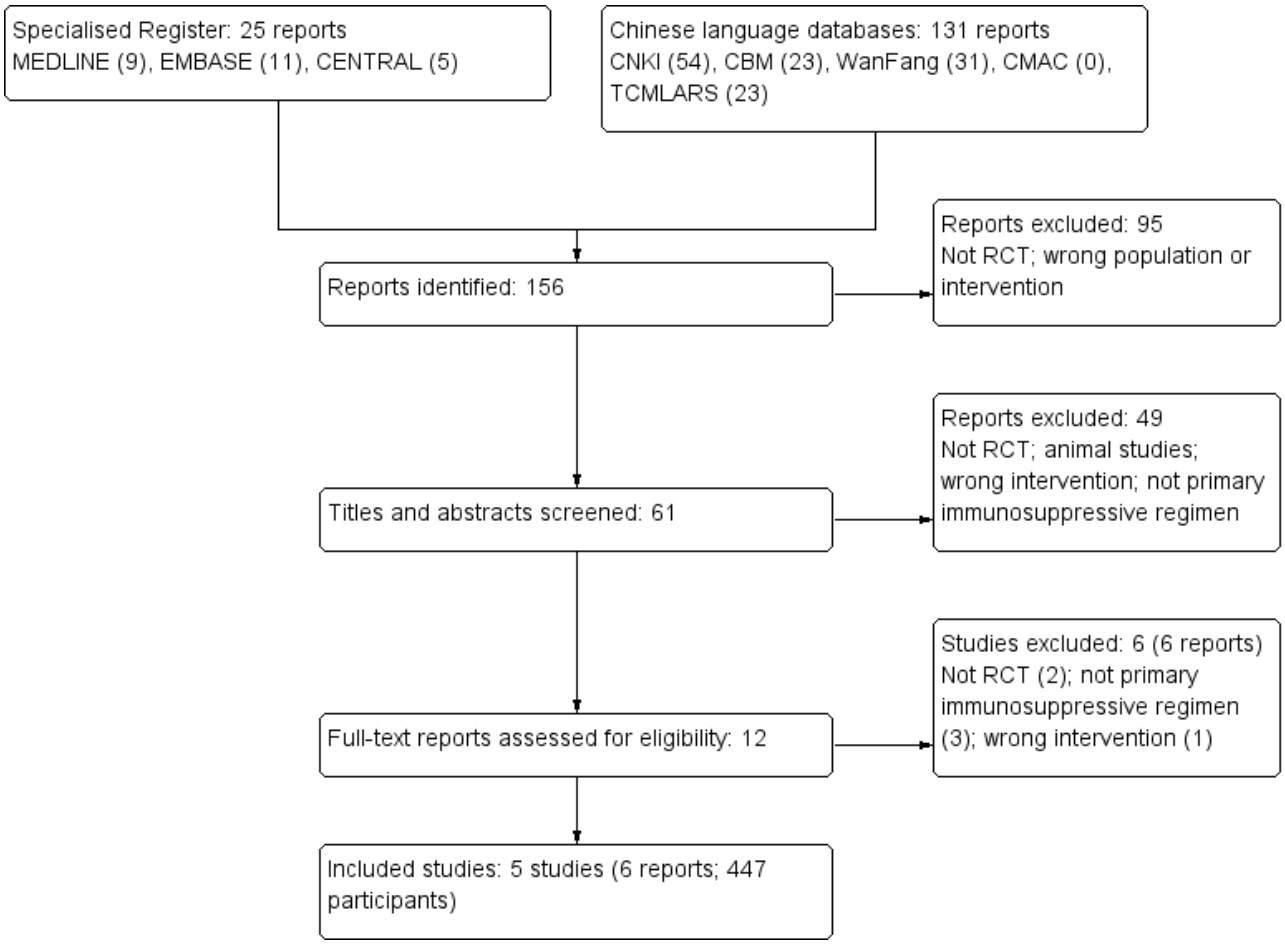
RESULTS

Description of studies

Results of the search

The search of the Cochrane Kidney and Transplant Specialised Register to 7 September 2015 identified 25 citations, and the combined search of databases in Chinese (CNKI, CBM, and WanFang, CMAC, TCMLARS) identified 131 citations. After duplicate reported were excluded then titles and abstracts reviewed, 12 reports underwent full-text review and we identified five studies (six reports) that met our inclusion criteria (Figure 1).

Figure 1. Study flow diagram



The five included studies reported data from 447 participants (214/233 treatment/control) (Ding 2011; Sun 2004a; Wang 2005; Wang 2005a; Yu 1991; see Characteristics of included studies).

Included studies

Of the five included studies, four investigated Cordyceps versus AZA (Sun 2004a; Wang 2005; Wang 2005a; Yu 1991) and one study (Ding 2011) investigated Cordyceps plus low dose CsA versus standard dose CsA. All were parallel design, single centre studies conducted in China. None of the included studies reported all outcomes of interest to this review. Authors of all included studies were contacted for clarification of characteristics of study methods and unreported data; however, no additional information was obtained.

Cordyceps was assessed as part of initial maintenance immunosuppression therapy following kidney transplantation in all studies. None of the study participants received Induction therapy. The Cordyceps preparation administered in all included studies was Bailing capsule (Hangzhou Pharmaceutical Co Ltd China), which is a dry powder from artificially fermented *Cordyceps sinensis.*

Cordyceps versus AZA

Sun 2004a, Wang 2005, Wang 2005a and Yu 1991 investigated Cordyceps versus AZA. There were 265 participants enrolled between 1989 and 2003, and all studies were published in Chinese medical journals.

Cordyceps dose ranged from 3.0 to 6.0 g/d and AZA from 50 to 150 mg/d. Baseline immunosuppression was maintained across both arms in all studies. During the transplant surgical period (from the day before surgery to the second day post-transplant) the same immunosuppression therapy, including CsA and prednisolone, were administered for all participants. All participants commenced therapy from the third day after transplantation. Concomitant therapy consisted of CsA and steroids.

Sun 2004a reported that the CsA dose was commenced at 150 mg/d from the third day following surgery and was adjusted according to SCr level and serum CsA concentration over the following 12 months. Wang 2005, Wang 2005a and Yu 1991 reported CsA administered at 7 mg/kg/d commencing from day 3 following surgery that was gradually reduced to 4 mg/kg/d at 12 months. However, detailed dose adjustment information was not reported (Characteristics of included studies).

Follow-up duration was one year in all studies. However, Yu 1991 reported one year follow-up for only 13/34 participants; the remainder of participants had been enrolled for less than one year before study end.

Transplant-focused outcomes were reported more frequently: graft loss was reported in four studies (Sun 2004a; Wang 2005; Wang 2005a; Yu 1991) and acute rejection in three (Sun 2004a; Wang 2005; Yu 1991); complications of immunosuppression including infection, anaemia and leucopenia were reported by Sun 2004a.

Graft survival was generally not defined; reporting on acute rejection was in terms of rejection episodes (Ding 2011; Sun 2004a; Wang 2005; Yu 1991).

Some outcomes were reported at different time points. Yu 1991 measured SCr reported as ordinal data (SCr incidence < 2 mg/dL, 2 to 2.5 mg/dL, or > 2 mg/dL) at three months post-transplantation. Sun 2004a reported SCr as continuous data (mean ± SD) at one year post-transplant, therfore these data could not be pooled for analysis. Yu 1991 reported leucopenia incidence and abnormal liver function (dichotomous data) at three months post-transplantation; however Sun 2004a reported leucocyte numbers and AST and ALT levels (continuous data) at one year post-transplantation. Thus, these data could not be pooled. Routine urinalysis (urinary erythrocytes, leucocytes) and blood tests (erythrocytes and white blood cell count) were reported only by Sun 2004a. Yu 1991 and Wang 2005 reported patient survival; no deaths were reported.

Blinding of interventions, investigators and outcome assessors were not reported. Most studies did not report study methodology in sufficient detail to enable assessment of all potential sources of bias, leading to a high proportion of unclear classifications.

Cordyceps with low dose CsA versus standard dose CsA

Ding 2011 (182 participants) compared Cordyceps with low dose CsA versus standard dose CsA from 2005 to 2007. All participants received immunosuppressive therapy (methylprednisolone 3.0 g and cyclophosphamide) for five days from surgery (day 1) to postoperative day 4. Cordyceps (3.0 g/d) and CsA (2.0 to 4.5 mg/kg/d) were commenced from day 5. Concomitant therapy included mycophenolate mofetil (MMF) and steroids. CsA was commenced at 4.5 mg/kg/d in both study arms, and gradually adjusted according to kidney and liver function from the second to 12 months following transplantation. CsA dose was 0.2 to 0.4 mg/kg/d lower in the Cordyceps treatment group than control group participants from the second to twelfth month post-transplant. No induction therapy was used. Follow-up duration was 12 months.

Ding 2011 reported several outcomes relevant to this review, including patient survival, graft survival, and acute rejection, as well as secondary outcomes, such as graft function, CNI nephrotoxicity, pulmonary infection, hepatotoxicity, liver function, CsA dose and blood concentration. Acute rejection episodes and CNI nephrotoxicity were confirmed by percutaneous kidney transplant biopsy. Episodes of acute rejection, incidence of nephrotoxicity and pulmonary infection, and CsA dose data were shown as graphs in the study report; primary digital data were unavailable through contact to author, so we extracted data using Engauge Digitizer planimetric software (version 4.1, Sourceforge.net).

Methodology reporting in Ding 2011 was suboptimal. Blinding to the intervention, investigators and outcome assessors were not reported.

Excluded studies

We excluded six studies (Ding 2009; Min 1996; Xu 1995; Xu 1997; Zhang 2008; Zhang 2011) following full-text assessment (Characteristics of excluded studies). Reasons for exclusion included: not RCT (2); investigated a different intervention, or Cordyceps was investigated as a secondary intervention (4).

Risk of bias in included studies

Overall, study methods were poorly reported (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

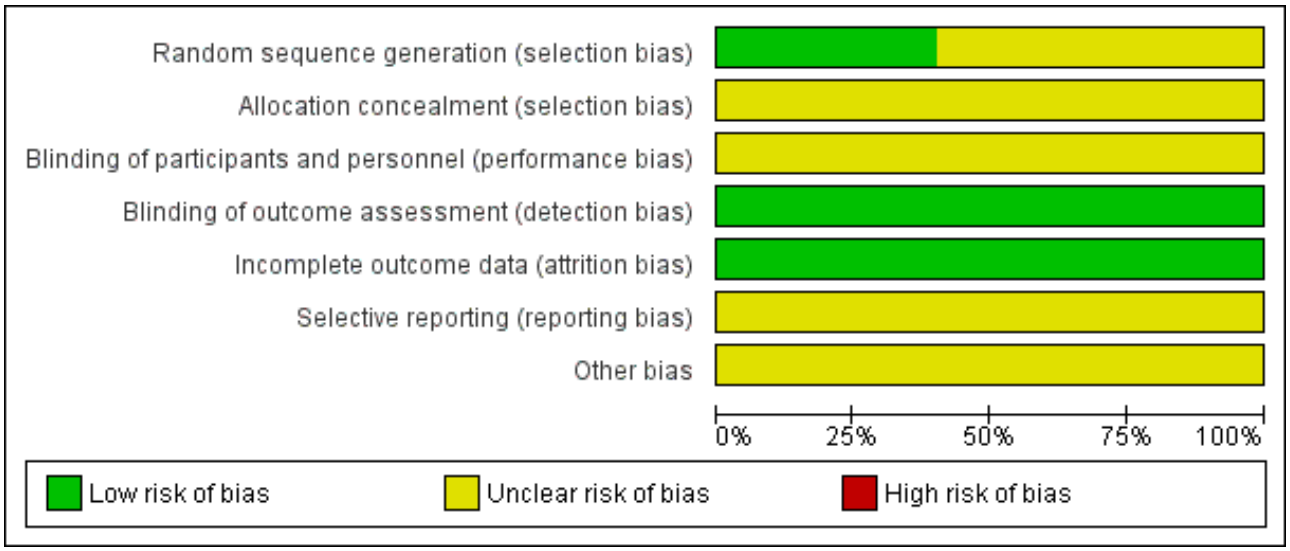
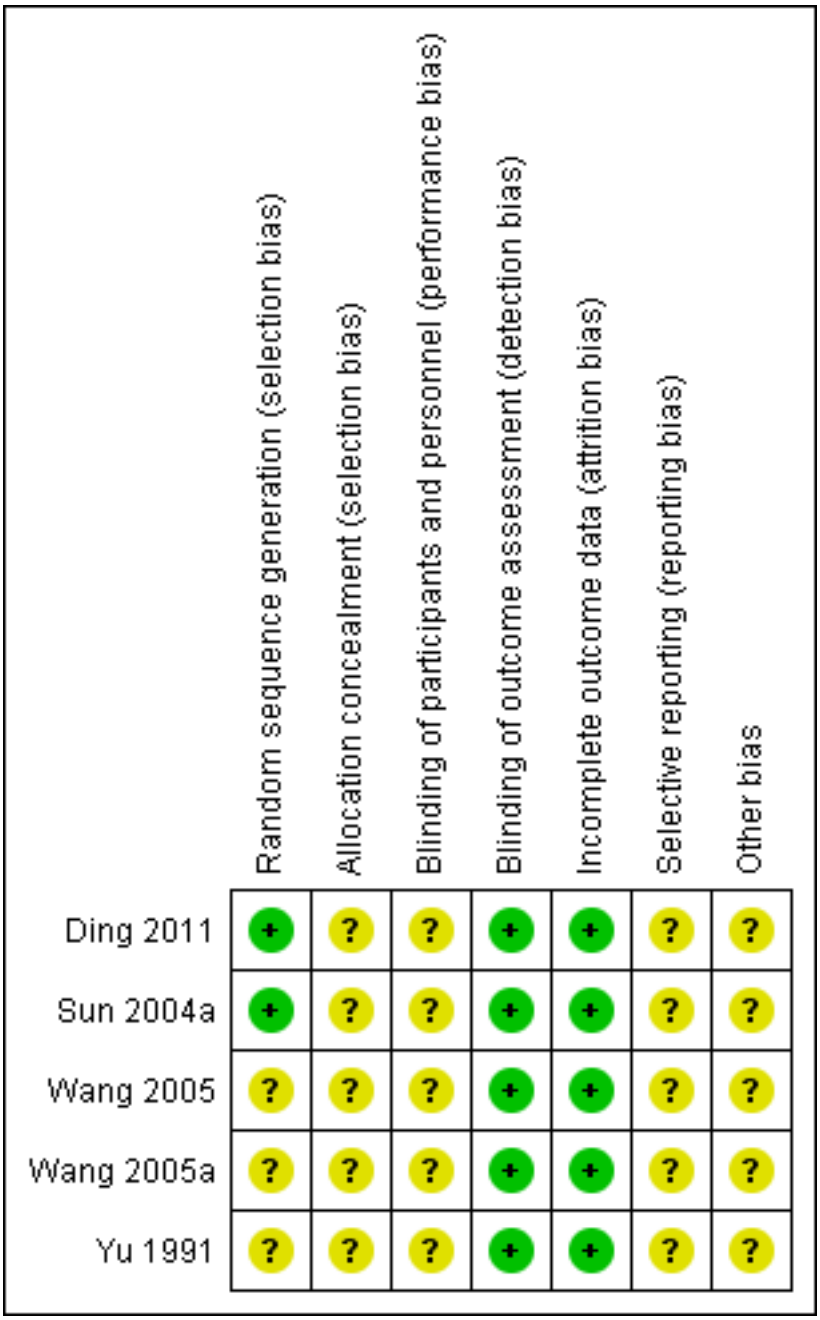


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

All included studies were reported as randomised; however, only Ding 2011 and Sun 2004a reported use of random number tables. Wang 2005, Wang 2005a and Yu 1991 did not report randomisation methods. None of the included studies reported allocation concealment. Selection bias was therefore assessed as unclear.

Blinding

Blinding of participants and outcomes assessments were not reported in any of the included studies; however, because most outcome data were obtained from objective medical records, our assessment was that lack of blinding of outcomes assessment was unlikely to introduce detection bias. Risk of detection bias in these studies was therefore assessed as low.

Incomplete outcome data

All studies reported follow-up. There were no missing outcome data, and risk of attrition bias was assessed as low. Follow-up of 21 of 34 participants in Yu 1991 was less than 12 months, and these data were excluded from our analyses.

Selective reporting

No study protocols were available for the included studies; it could not be determined if published reports included all expected

outcomes. Intention-to-treat analysis was not reported or apparent for all included studies. Risk of selective reporting bias was assessed as unclear.

Other potential sources of bias

No studies reported funding sources; it was not possible to determine if they were free of funding or other bias.

Effects of interventions

Cordyceps versus AZA

Of the five included studies, four investigated Cordyceps versus AZA (Sun 2004a; Wang 2005; Wang 2005a; Yu 1991).

Patient survival

Yu 1991 and Wang 2005 (55 participants) reported patient survival. No deaths were reported during the first year following transplantation.

Graft survival

There was no significant difference in graft loss at one year (Analysis 1.1; (4 studies, 244 participants): RR 0.81, 95% CI 0.31 to 2.10; I^2 = 0%).

Acute rejection

There was less acute rejection in the Cordyceps group one year after transplantation, however the difference was not statistically significant (Analysis 1.2 (3 studies, 197 participants): RR 0.72, 95% CI 0.44 to 1.18; I^2 = 0%).

Kidney function

Only Sun 2004a reported graft function quantitatively. At one year post-transplant SCr was significantly lower among participants in the Cordyceps treatment arm compared with AZA (Analysis 1.3 (1 study, 121 participants): MD -15.00 µmol/L, 95% CI -27.73 to -2.27). GFR was not reported in any of the studies.

Complications and side effects of immunosuppression

Sun 2004a reported less infections in the Cordyceps group one year after transplantation, however the difference was not statistically significant (Analysis 1.4 (1 study, 121 participants): RR 0.79, 95% CI 0.50 to 1.26).

At one year post-transplantation, Sun 2004a reported the mean WBC and RBC counts for participants in the AZA group were abnormally low and reached 3.9 x 10^9/L and 3.6 x 10^{12}/L respectively. Cordyceps-treated participants had significantly higher blood counts compared to the AZA group (Analysis 1.5 (121 participants): MD 2.50 x 10^9/L WBC, 95% CI 2.03 to 2.97; Analysis 1.6 (121 participants): MD 1.00 x 10^{12}/L RBC, 95% CI 0.75 to 1.25).

Sun 2004a reported liver enzymes (AST, ALT) in the AZA group were abnormally elevated and reached 52.3 U/L and 46.8 U/L respectively at one year. Cordyceps-treated participants had significantly lower levels compared to the AZA group (Analysis 1.7 (121 participants): MD -17.60 U/L AST, 95% CI -23.11 to -12.09; Analysis 1.8 (121 participants): (MD -15.30 U/L ALT, 95% CI -20.51 to -10.09).

No other adverse reactions to drug administration (such as malignancy, cytomegalovirus disease, or CIN-related nephrotoxicity) were reported.

Quality of life

Quality of life measures were not reported.

Cordyceps plus low dose CsA versus standard dose CsA

Ding 2011 investigated Cordyceps with low dose CsA. Although the study included 182 participants, recipients who died or experienced allograft function loss and nephrotoxicity were excluded from the kidney function analysis. Data from 109 participants were reported in terms of kidney function, CsA dose and blood concentration. Participants with hepatotoxicity were excluded from analyses of liver function.

Patient survival

Ding 2011 reported no significant difference in all-cause mortality between the Cordyceps and control groups one year post-transplantation (Analysis 2.1 (182 participants): RR 0.60, 95% CI 0.11 to 3.17).

Graft survival

There was no significant difference reported in graft loss between the Cordyceps and control groups one year post-transplantation (Analysis 2.2 (182 participants): RR 0.80, 95% CI 0.23 to 2.72).

Acute rejection

Ding 2011 reported no significant difference in acute rejection (confirmed by percutaneous kidney transplant biopsy) between the Cordyceps and control groups one year post-transplantation (Analysis 2.3 (182 participants): RR 0.80, 95% CI 0.38 to 1.68).

Kidney function

There was no significant difference reported in SCr between the Cordyceps and control groups one year post-transplantation (Analysis 2.4 (109 participants): -5.62 µmol/L; 95% CI -14.84 to 3.60). GFR was not reported.

CsA dose and blood concentration

Differences in CsA dose between groups was not significant at one month post-transplantation; however from two to 12 months, the CsA dose for Cordyceps participants was significantly lower than control group participants. No significant differences were observed in whole blood trough CsA concentrations at one to two months post-transplantation.

Ding 2011 reported whole blood trough CsA concentrations in the Cordyceps group were significantly lower than control group at three months (Analysis 2.5.1 (109 participants): -34.1 µg/L; 95% CI -55.73 to -12.47), six months (Analysis 2.5.2 (109 participants): -17.90 µg/L; 95% CI -31.85 to -3.95), and at one year (Analysis 2.5.3 (109 participants): -12.60 µg/L; 95% CI -19.99 to -5.21).

Complications and side effects of immunosuppression

Ding 2011 reported participants who received Cordyceps plus low dose CsA treatment showed a significantly lower incidence of pulmonary infection compared with the control group at one year (Analysis 2.6 (182 participants): RR 0.43, 95% CI 0.19 to 0.96).

Ding 2011 reported less CNI nephrotoxicity (confirmed by percutaneous kidney transplant biopsy) in the Cordyceps plus low dose CsA group at one year, however the difference was not statistically significant (Analysis 2.7 (182 participants): RR 0.50, 95% CI 0.24 to 1.04).

Liver enzymes were significantly lower in the Cordyceps plus low dose CsA group compared to the control group (Analysis 2.8 (136 participants): MD -5.70 U/L AST, 95% CI -9.95 to-1.45) (Analysis 2.9 (136 participants): MD -3.80 U/L ALT, 95% CI -7.63 to 0.03).

Ding 2011 reported Cordyceps plus low dose CsA significantly increased serum albumin compared to the control group (Analysis 2.10 (136 participants): 5.50 µmol/L; 95% CI 1.05 to 9.95). Serum uric acid was significantly lower in the Cordyceps plus low dose CsA group compared to the control group (Analysis 2.11 (109 participants): -84.19 µmol/L; 95% CI -117.86 to -50.52) compared with control. Serum albumin was used as a liver function marker. In their assessment of serum albumin levels Ding 2011 excluded recipients who had died or experienced allograft function loss and hepatotoxicity. Serum uric acid was used as a kidney function marker, and similarly, recipients who had died or experienced allograft function loss and nephrotoxicity were excluded from the analyses.

No other adverse reactions to drug administration were reported.

Quality of life

Quality of life measures were not reported.

DISCUSSION

Summary of main results

We included five studies (6 reports; 447 participants) that assessed the effects of Cordyceps as adjuvant therapy in initial maintenance immunosuppression for kidney transplantation recipients conducted at hospitals in China. Suboptimal methods and data reporting meant that overall the included studies were assessed as having unclear risks of bias.

Compared with AZA, Cordyceps significantly improved kidney function (SCr) and incidence of acute rejection during the first year following transplantation was less, however this was not significant. Mortality and graft survival did not differ between the treatment groups in the first year post-transplantation. Limited evidence suggested that compared with AZA, Cordyceps improved anaemia and leucopenia, decreased liver enzymes, and may reduce incidence of infection (Sun 2004a; Wang 2005; Wang 2005a; Yu 1991).

Only one study compared Cordyceps with low dose CsA versus standard dose CsA. Ding 2009 did not report any statistically significant differences between arms in relation to patient survival, graft loss, acute rejection, or allograft function within the first year post-transplantation. Cordyceps was associated with benefits in reducing pulmonary infection, serum albumin and uric acid levels, and liver enzymes. CNI nephrotoxicity was less in the Cordyceps and low CsA group. These benefits may either be due to Cordyceps' protective effects, or simply due to lower CsA exposure.

Overall completeness and applicability of evidence

We were unable to obtain data relating to all predefined outcomes because of lack of reporting. Overall, outcome reporting was suboptimal: in four studies that compared Cordyceps versus AZA, two reported on patient survival, four on graft loss, three on acute rejection, two on adverse events, and only one study reported on infection, anaemia, leucopenia, and liver enzymes. None of included studies reported quality of life outcomes.

In the past decade, more powerful immunosuppressive drugs have become available which are widely used for kidney transplant recipients. However, we did not find any studies that investigated other more aggressive drugs, such as tacrolimus or induction therapy. We did not find RCTs comparing Cordyceps versus MMF or Cordyceps with low dose tacrolimus versus standard dose tacrolimus. Cordyceps was assessed as part of initial maintenance immunosuppression therapy in all studies. None of the study participants received Induction therapy.

Quality of the evidence

The quality and quantity of available evidence limited our findings and interpretations. Limited numbers of participants were included in five studies, and therefore, risks of random errors potentially explain occasional significant effects in individual studies. In addition, all participants were Chinese and therefore may not be representative of the global population of kidney transplant recipients.

All included studies were of short duration (three months to one year), so it was not possible to elicit evidence relating to longer-term effects of Cordyceps on outcome measures. Long-term effects in terms of mortality, graft loss, chronic allograft injury, infection, and malignancy would be particularly valuable.

We explored statistical heterogeneity using the Chi^2 test and measured heterogeneity using I^2 test. When studies are small or few in number, as in this review, the power of the Chi^2 test in meta-analyses is limited. Hence, we looked at both fixed-effect and random-effects models to provide more conservative effect estimates; no differences were seen for outcome measures considered in this review. Because many outcomes involved few patients and events, the precision of our results was influenced, and accordingly, confidence intervals were wide.

Potential biases in the review process

Studies assessed at high risk of bias tend to overestimate beneficial intervention effects. Of the five included studies, important methodological details (such as allocation concealment and blinding) were seldom reported. The risk of systematic errors that might stem from these design and methodological defects were therefore difficult or impossible to assess with precision. It is possible that estimated intervention effects, especially significant beneficial effects, could be attributable to systematic errors.

The paucity and small sample size of available studies meant that risk of random error was high and the ability to detect the true beneficial or harmful effects associated with the use of Cordyceps was considerably weakened for this review.

Agreements and disagreements with other studies or reviews

A recent longer-term (three to five year follow-up) retrospective clinical study involving 180 kidney transplantation recipients (Wang 2013) compared Cordyceps (Bailing capsules) (80) versus no drug (100). Participant groups did not differ significantly in demographic or immunological parameters (age, gender, cold ischaemia time, donor–recipient human leukocyte antigen typing, lymphocytotoxicity testing, and use of immunosuppressive agents). There was no significant difference in incidence of acute rejection between the groups. One and five-year kidney allograft survival rates were 97.5% and 95.0% respectively in the Cordyceps group, and 92.5% and 84% respectively in control group. Differences in kidney allograft survival were statistically significant at five years post-transplantation. Although one and five year patient survival rates were 98.7% and 98.0% respectively in the Cordyceps group, and 95.0% and 93.0% respectively in control group, the differences were not statistically significant. Participants in the Cordyceps group had lower incidence rates of infection, liver enzymes, total bilirubin, and uric acid and higher peripheral red and white blood cell counts than control group participants. Although our analysis found similar outcomes, it is uncertain if short-term trends could translate to long-term benefits.

There were few studies (Zhang 2008; Zhang 2011) that investigated the effect of Cordyceps on chronic allograft nephropathy in kidney transplant recipients. Zhang 2011 involved 231 participants and compared Cordyceps with standard care (traditional immunosuppressive agents only), with traditional immunosuppressive drug baseline in both arms. Cordyceps treatment significantly improved SCr and CrCl, but no significant improvement was observed in the control group. No adverse effects (acute rejection, infection, impairment of liver function, and reduction of white blood cell count) were observed in the Cordyceps group. These results suggest that Cordyceps may provide some protection of allograft kidney function from chronic injury in kidney transplantation recipients.

We found no evidence that Cordyceps had been used as part of immunosuppressive therapy for other solid organ transplant recipients.

AUTHORS' CONCLUSIONS

Implications for practice

Compared with AZA, Cordyceps showed no difference in mortality and graft loss, but was associated with some improvement in graft function, anaemia, leucopenia, and liver function injury. There was limited evidence to suggest that Cordyceps may reduce acute rejection and infection rates. The results from one study indicated that compared with standard dose CsA, Cordyceps with low dose CsA did not significantly differ in terms of mortality, graft loss, acute rejection, or allograft function. Positive effects were indicated in relation to pulmonary infection, serum albumin and uric acid levels. These benefits could simply be due to lower CsA exposure rather than any protective effect of Cordyceps.

All results should be interpreted with caution: we identified limitations relating to the quality, number, size, duration, and nature of included studies. The marginal benefits shown could equally be due to lower doses of CNI or AZA, both of which have proven dose-related toxicities. Potentially positive effects attributed to Cordyceps need to be investigated further and clarified.

Implications for research

All included studies were of short duration. It remains unclear if short-term beneficial effects identified can be maintained and translated into the longer-term. Furthermore, because many events (such as malignancy, death, allograft failure) are more likely to occur beyond 12 months post-transplantation, longer-term studies are needed to confirm this possibility.

Further comprehensive investigation is warranted to establish if Cordyceps with, or in place of a component of traditional immunosuppressive therapy (such as CNI and an antiproliferative agent with or without corticosteroids), would achieve sufficient immunosuppression and minimise drug-related toxicity. Future studies should investigate Cordyceps use in immunosuppressive therapies using tacrolimus, MMF, or induction therapy.

The mechanisms of action of Cordyceps need to be explored in experimental studies: its active components and biological activity need to be identified. The mechanism of action for some effects remains unknown.

Appropriately sized and powered RCTs investigating the effects of Cordyceps in immunosuppressive therapy for kidney transplantation recipients need to be considered. Such studies should be planned and conducted to ensure low risk of systematic and random errors, and apply the CONSORT guidelines.

ACKNOWLEDGEMENTS

We would like to thank:

- The referees for comments and feedback during the preparation of this review.
- Cochrane Kidney and Transplant for their kind assistance in preparing this review.
- The investigators and participants of the included studies. Without their initiative we would have nothing to review.

REFERENCES

References to studies included in this review

Ding 2011 *{published data only}*

Ding C, Tian PX, Xue W, Ding X, Yan H, Pan X, et al. Efficacy of Cordyceps sinensis in long term treatment of renal transplant patients. *Frontiers in Bioscience* 2011;**3**:301-7. [MEDLINE: 21196310]

Li Y, Xue WJ, Tian PX, Ding XM, Yan H, Pan XM, et al. Clinical application of Cordyceps sinensis on immunosuppressive therapy in renal transplantation. *Transplantation Proceedings* 2009;**41**(5):1565-9. [MEDLINE: 19545680]

Sun 2004a *{published data only}*

Sun M, Yang YR, Lu YP, Gao R, Wang L, Wang J, et al. Clinical study on application of bailing capsule after renal transplantation. *Zhongguo Zhongxiyi Jiehe Zazhi [Chinese Journal of Integrated Traditional & Western Medicine]* 2004;**24**(9):808-10. [MEDLINE: 15495826]

Wang 2005 *{published data only}*

Wang YG. Analysis of amelioration of function of transplanted renal by Bailing capsule. *Zhongguo Zhong Xi Yi Jie He Wai Ke Za Zhi [Chinese Journal of Surgery of Integrated Traditional & Western Medicine]* 2005;**11**(4):332-3.

Wang 2005a *{published data only}*

Wang YP. Observation of efficacy of Bailing capsule in long term treatment of renal transplant patients. *Huaxi Yixue [West China Medical Journal]* 2005;**17**(6):563.

Yu 1991 *{published data only}*

Yu HY, Zhu XY. Cultivated Cordyceps sinensis (Q80) as an immunosuppressive in renal transplantations. *Zhonghua Mi Niao Wai Ke Za Zhi [Chinese Journal of Urology]* 1991;**12**:328-31.

References to studies excluded from this review

Ding 2009 *{published data only}*

Ding CG, Tian PX, Jin ZK. Clinical application and exploration on mechanism of action of Cordyceps sinensis mycelia preparation for renal transplantation recipients. *Zhongguo Zhongxiyi Jiehe Zazhi [Chinese Journal of Integrated Traditional & Western Medicine]* 2009;**29**(11):975-8. [MEDLINE: 20329604]

Min 1996 *{published data only}*

Min Z, Oi J, Zhu Y, Wei W. Application of Corbrin capsule in human renal transplantation. *Transplantation Proceedings* 1996;**28**(3):1626-8. [MEDLINE: 8658813]

Xu 1995 *{published data only}*

Xu F, Huang JB, Jiang L, Xu J, Mi J. Amelioration of cyclosporin nephrotoxicity by Cordyceps sinensis in kidney-transplanted recipients. *Nephrology Dialysis Transplantation* 1995;**10**(1):142-3. [MEDLINE: 7724020]

Xu 1997 *{published data only}*

Xu F, Wu C, Zhang Z, Zhou H. Amelioration of cyclosporine A nephrotoxicity by calcium antagonists. *Zhongguo Linchuang Yaolixue Zazhi [Chinese Journal of Clinical Pharmacology]* 1997;**13**(1):27-31.

Zhang 2008 *{published data only}*

Zhang ZH, Zhang WD, Yao K. Treatment of chronic allograft nephropathy with combination of enalapril and bailing capsule. *Zhongguo Zhongxiyi Jiehe Zazhi [Chinese Journal of Integrated Traditional & Western Medicine]* 2008;**28**(9):806-9. [MEDLINE: 19065894]

Zhang 2011 *{published data only}*

Zhang Z, Wang X, Zhang Y, Ye G. Effect of Cordyceps sinensis on renal function of patients with chronic allograft nephropathy. *Urologia Internationalis* 2011;**86**(3):298-301. [MEDLINE: 21335937]

Additional references

Chai 2009

Chai JJ, Chen YP, Rui HL. Effects of Hirsutella sinensis on TGF-beta1 and Snail expressions and transdifferentiation of tubular epithelial-myofibroblast in renal tissue of rats with chronic aristolochic acid nephropathy. *Zhongguo Zhongxiyi Jiehe Zazhi [Chinese Journal of Integrated Traditional & Western Medicine]* 2009;**29**(4):325-9. [MEDLINE: 19526758]

Cheng 2006

Cheng DW, Zou Y, Qian N, Wang CL, Tian YB, Wang DL, et al. Effects of compound preparation of Cordyceps sinensis and Tripterygium hypoglaucum on survival time of pigskin after allogeneic transplantation. *Zhong Xi Yi Jie He Xue Bao [Journal of Chinese Integrative Medicine]* 2006;**4**(2):185-8. [MEDLINE: 16529697]

de Mattos 2000

de Mattos AM, Olyaei AJ, Bennett WM. Nephrotoxicity of immunosuppressive drugs: long-term consequences and challenges for the future. *American Journal of Kidney Diseases* 2000;**35**(2):333-46. [MEDLINE: 10676738]

Ding 2009a

Ding C, Tian P, Jia L, Li Y, Ding X, Xiang H, et al. The synergistic effects of C. Sinensis with CsA in preventing allograft rejection. *Frontiers in Bioscience (Landmark Edition)* 2009;**14**:3864-71. [MEDLINE: 19273316]

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60. [MEDLINE: 12958120]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Jian 1995

Jian JY, Hu SM, Hong WH, Huang JM. Toxicological study of Cordyceps sinensis artificially cultivated. *Weisheng Yanjiu [Journal of Hygiene Research]* 1995;**24**:74-7.

Jiang 1995

Jiang BJ, Kong XH, Wang HQ, Yin XJ, Liu LJ, Ma ZJ, Wang H. Toxicological study of Cordyceps Sinensis cultivated by artificial fermentation on its safety evaluation, I. acute and sub-chronic toxicity studies. *Journal of Capital Institute of Medicine* 1995;**16**(3):198-203.

Jordan 2008

Jordan JL, Hirsch GM, Lee TD. C. sinensis ablates allograft vasculopathy when used as an adjuvant therapy with cyclosporin A. *Transplant Immunology* 2008;**19**(3-4):159-66. [MEDLINE: 18619544]

Ka 2006

Ka Wai Lee S, Kwok Wong C, Kai Kong S, Nam Leung K, Wai Kei Lam C. Immunomodulatory activities of HERBSnSENSES Cordyceps - in vitro and in vivo studies. *Immunopharmacology & Immunotoxicology* 2006;**28**(2):341-60. [MEDLINE: 16873101]

Kong 1995

Kong XH, Jiang BJ, Wang HQ, Yin XJ, Tang YP, Ma ZJ, et al. Toxicological study of Cordyceps Sinensis cultivated by artificial fermentation on its safety evaluation, II. mutagenicity study. *Journal of Capital Institute of Medicine* 1995;**16**(4):256-258.

Li 2009

Li Y, Xue WJ, Tian PX, Ding XM, Yan H, Pan XM, et al. Clinical application of Cordyceps sinensis on immunosuppressive therapy in renal transplantation. *Transplantation Proceedings* 2009;**41**(5):1565-9. [MEDLINE: 19545680]

Luo 2007

Luo ZJ, Cheng DW, Lian LH. Effect of Cordyceps sinensis compound on immunologic rejection function in mouse. *Shiyong Yixue Zazhi [Journal of Practical Medicine]* 2007;**23**(15):2313-6.

Meier-Kriesche 2004

Meier-Kriesche HU, Schold JD, Srinivas TR, Kaplan B. Lack of improvement in renal allograft survival despite a marked decrease in acute rejection rates over the most recent era. *American Journal of Transplantation* 2004;**4**(3):378-83. [MEDLINE: 14961990]

Nankivell 2003

Nankivell BJ, Borrows RJ, Fung CL, O'Connell PJ, Allen RD, Chapman JR. The natural history of chronic allograft nephropathy. *New England Journal of Medicine* 2003;**349**(24):2326-33. [MEDLINE: 14668458]

Olyaei 2001

Olyaei AJ, de Mattos AM, Bennett WM. Nephrotoxicity of immunosuppressive drugs: new insight and preventive strategies. *Current Opinion in Critical Care* 2001;**7**(6):384-9. [MEDLINE: 11805539]

OPTN 2015

US Department of Health & Human Services. Organ Procurement & Transplantation Network. optn.transplant.hrsa.gov/ (accessed 1 October 2054).

Shin 2001

Shin KH, Lim SS, Lee SH, Lee YS, Cho SY. Antioxidant and immunostimulating activities of the fruiting bodies of Paecilomyces japonica, a new type of Cordyceps sp. *Annals of the New York Academy of Sciences* 2001;**928**:261-73. [MEDLINE: 11795517]

Sun 2004

Sun M, Yang YR, Lu YP, Gao R, Wang L, Wang J, et al. Clinical study on application of bailing capsule after renal transplantation. *Zhongguo Zhongxiyi Jiehe Zazhi [Chinese Journal of Integrated Traditional & Western Medicine]* 2004;**24**(9):808-10. [MEDLINE: 15495826]

Vella 2010

Vella J, Brennan DC. Chronic renal allograft nephropathy. uptodate.com (accessed 1 October 2015).

Wang 2013

Wang W, Zhang XN, Yin H, Li XB, Hu XP, Liu H, et al. Effects of Bailing capsules for renal transplant recipients: a retrospective clinical study. *Chinese Medical Journal* 2013;**126**(10):1895-9. [MEDLINE: 23673106]

Yamaguchi 2000

Yamaguchi Y, Kagota S, Nakamura K, Shinozuka K, Kunitomo M. Inhibitory effects of water extracts from fruiting bodies of cultured Cordyceps sinensis on raised serum lipid peroxide levels and aortic cholesterol deposition in atherosclerotic mice. *Phytotherapy Research* 2000;**14**(8):650-2. [MEDLINE: 11114007]

Zhang 1990

Zhang Z, Xia SS. Cordyceps sinensis-I as an immunosuppressant in heterotopic heart allograft model in rats. *Journal of Tongji Medical University* 1990;**10**(2):100-3. [MEDLINE: 2213952]

Zhao 1993

Zhao X, Li L. Cordyceps sinensis in protection of the kidney from cyclosporine A nephrotoxicity. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* 1993;**73**(7):410-2, 447. [MEDLINE: 8293343]

Zhao 2007

Zhao S, Zhang WH, Fu YM, Cui HZ, Chi YM. Effects of Astragalus polysaccharides and Cordyceps sinensis mycelium mixture on the transforming growth factor-beta1 expression in chronic rejection of artery transplantation: experiment with rats. *Chung-Hua i Hsueh Tsa Chih [Chinese Medical Journal]* 2007;**87**(12):851-4. [MEDLINE: 17565873]

Zhu 1998a

Zhu JS, Halpern GM, Jones K. The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis: part I. *Journal of Alternative & Complementary Medicine* 1998;**4**(3):289-303. [MEDLINE: 9764768]

Zhu 1998b

Zhu JS, Halpern GM, Jones K. The scientific rediscovery of a precious ancient Chinese herbal regimen: Cordyceps sinensis: part II. *Journal of Alternative & Complementary Medicine* 1998;**4**(4):429-57. [MEDLINE: 9884180]

References to other published versions of this review

Hong 2012

Hong T, Zhang M, Fan J. Cordyceps sinensis (a traditional Chinese medicine) for kidney transplant recipients. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD009698]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ding 2011

Methods	• Study design: parallel RCT • Time frame: January 2005 to December 2007 • Follow-up: 1 year
Participants	• Country: China • Setting: hospital • Number: treatment group (83); control group (99) • Mean age ± SD (years): treatment group (36.7 ± 11.7); control group (38.3 ± 10.6) • Sex (M/F): treatment group (65/18); control group (80/19)
Interventions	Treatment group • Cordyceps sinensis: 1.0 g, 3 times/d • Low dose CsA Control • Standard dose CsA Duration of intervention • 1 year Co-interventions • MMF + steroid
Outcomes	• One year patient and graft survival rate • Kidney function (SCr, BUN, uric acid) • 24h proteinuria • Blood trough CsA concentration • Liver function (ALB, AST, ALT, DBIL,TBIL) • Complications (acute rejection, hepatotoxicity, nephrotoxicity, pulmonary infection) • Serum cytokines (IL-2, IL-10)
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned by lot using a random number table to treatment and control groups

Ding 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was not reported, but the outcome were objective and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Sun 2004a

Methods	• Study design: parallel RCT • Time frame: 1999 to 2001 • Follow-up: 1 year
Participants	• Country: China • Setting: hospital • Number: treatment group (57); control group (64) • Mean age (years): treatment group (42.9); control group (40.5) • Sex (M/F): treatment group (39/18); control group (42/22)
Interventions	Treatment group • Cordyceps sinensis: 3 g/d Control group • AZA: 50 mg/d Duration of intervention • 1 year Co-interventions • CsA: started as 150 mg/d and then adjusted according to the level of SCr and CsA blood concentration • Prednisone: started as 80 mg/d, then reduced 10 mg every day, maintained with 20 mg/d, reduced to 10 mg/d after 1 year
Outcomes	• 1 year graft survival rate • Incidence of acute rejection • Kidney function (SCr, BUN) • Urinary RBC • Serum uric acid

Sun 2004a *(Continued)*

	• Liver function (ALB, AST, ALT) • Blood tests (RBC, WBC, platelets) • Complication incidence (infection) • Serum glucose level
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Divided into two groups according to random number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was not reported, but the outcome were objective and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Wang 2005

Methods	• Study design: parallel RCT • Time frame: April 1994 to October 2003 • Follow-up: 1 year
Participants	• Country: China • Setting: hospital • Number: treatment group (21); control group (21) • Mean age (years): treatment group (34.2); control group (35.2) • Sex (M/F): treatment group (16/5); control group (13/8)
Interventions	Treatment group • Cordyceps sinensis: 6 g/d and reduced to 3 g/d after 1 year Control group • AZA: 150 mg/d and reduced to 75 mg/d after 1 year Duration of intervention

Wang 2005 *(Continued)*

	• 1 year Co-interventions • CsA: 7 mg/kg/d and reduced to 4 mg/kg/d after 1 year • Prednisone: 30 mg/d and reduced to 10 mg/d after 1 year
Outcomes	• 1 year graft survival rate • Incidence of acute rejection • Incidence of reduction of WBC
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Divided randomly into two groups, but the method was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was not reported, but the outcome were objective and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Wang 2005a

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up: 1 year
Participants	• Country: China • Setting: hospital • Number: treatment group (36); control group (32) • Mean age (years): treatment group (45); control group (47) • Sex (M/F): treatment group (20/16); control group (18/14)
Interventions	Treatment group

Wang 2005a *(Continued)*

	• Cordyceps sinensis; doses not reported Control group • AZA: doses not reported Duration of intervention • 1 year Co-interventions • CsA: doses not reported • Prednisone: doses not reported
Outcomes	• 1 year graft survival rate
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomly assignation", but the method was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported, but the outcome were unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Yu 1991

Methods	• Study design: parallel RCT • Time frame: April 1989 to October 1990 • Follow-up: 3 months to 1 year
Participants	• Country: China • Setting: hospital • Number: treatment group (17); control group (17) • Mean age (years): treatment group (34.2); control group (35.2)

Yu 1991 *(Continued)*

	• Sex (M/F): treatment group (12/5); control group (13/4)
Interventions	Treatment group • Cordyceps sinensis: 5.2 g/d Control group • AZA: started as 150 mg/d and reduced to 75 mg/d after 1 year Duration of intervention • 1 year Co-interventions • CsA: started as 7 mg/kg/d and reduced to 4 mg/kg/d after 1 year • Prednisone: started as 30 mg/d and reduced to 10 mg/d after 1 year
Outcomes	• 1 year patient and graft survival rate • Incidence of acute rejection • Kidney function (SCr, 3 months after operation) • Liver function (ALT, 3 months after operation) • Incidence of reduction of WBC • Phagocytosis function of WBC • Activity of natural killer cells
Notes	• Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly divided into two groups, but method was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding was not reported, but the outcome were objective and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

ALB - albumin; ALT- alanine aminotransferase; AST- aspartate aminotransferase; AZA - azathioprine; BUN - blood urea nitrogen; CsA - cyclosporin A; DBIL - direct bilirubin; IL- interleukin; M/F - male/female; MMF - mycophenolate mofetil; RBC - red blood cell; RCT - randomised controlled trial; SCr - serum creatinine; SD - standard deviation; TBIL - total bilirubin; WBC - white blood cell

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ding 2009	Not RCT
Min 1996	Not RCT
Xu 1995	*Cordyceps sinensis* was used as a secondary regimen for stable kidney transplant recipients 3 months after transplantation. Study duration was only days
Xu 1997	*Cordyceps sinensis* was not investigated
Zhang 2008	*Cordyceps sinensis* was used as a secondary regimen for kidney transplant recipients with chronic allograft nephropathy. Outcomes reported were graft function (SCr) at 6 months and 9 months after treatment
Zhang 2011	*Cordyceps sinensis* was used as a secondary regimen for kidney transplant recipients with chronic allograft nephropathy

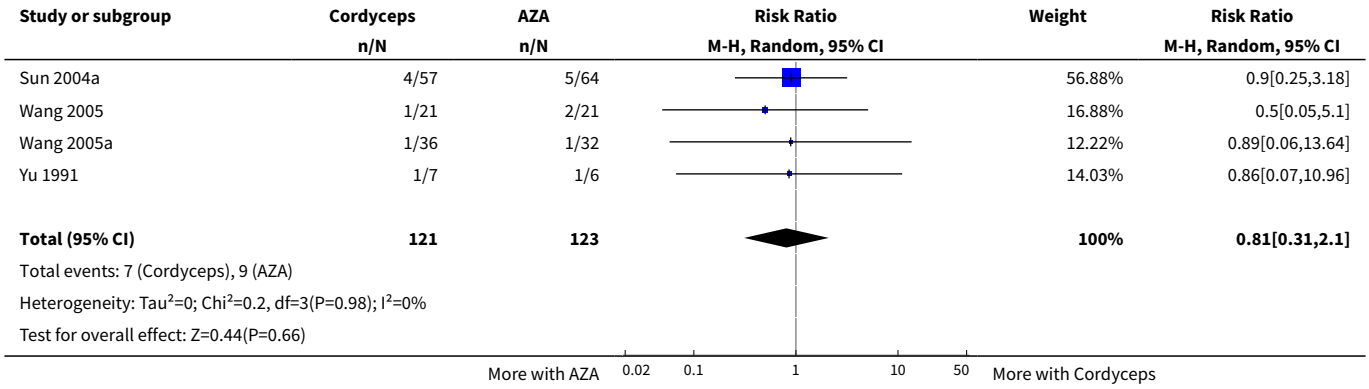
RCT - randomised controlled trial; SCr - serum creatinine

DATA AND ANALYSES

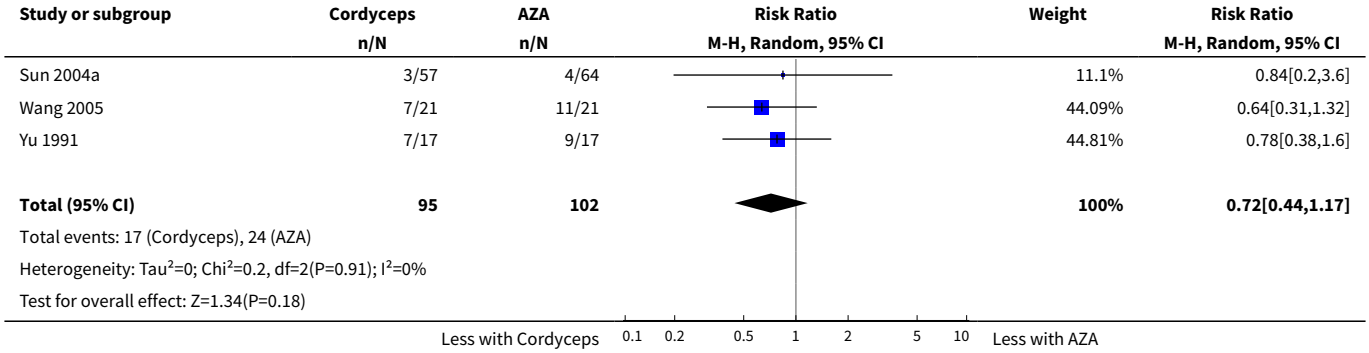
Comparison 1. *Cordyceps sinensis* versus azathioprine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Graft survival	4	244	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.31, 2.10]
2 Acute rejection	3	197	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.44, 1.17]
3 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Leukocytes	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Erythrocytes	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 AST	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 ALT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

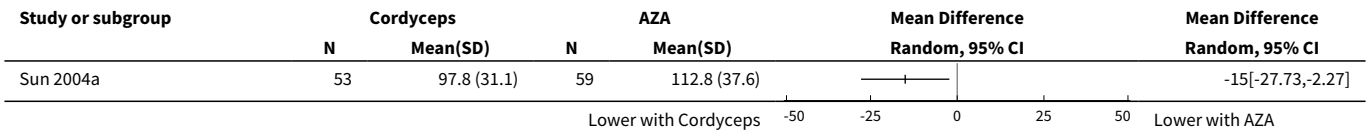
Analysis 1.1. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 1 Graft survival.



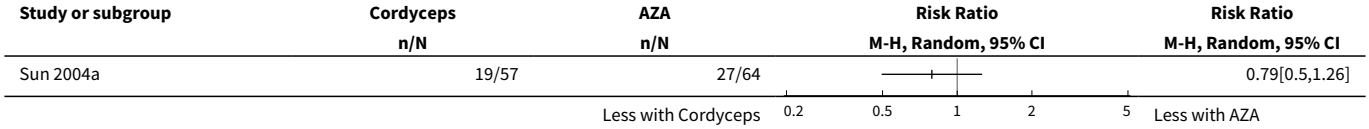
Analysis 1.2. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 2 Acute rejection.



Analysis 1.3. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 3 Serum creatinine.

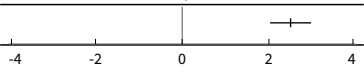


Analysis 1.4. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 4 Infection.



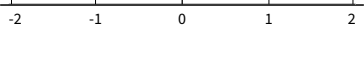
Analysis 1.5. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 5 Leukocytes.

Study or subgroup	Cordyceps N	Cordyceps Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sun 2004a	57	6.4 (1.5)	64	3.9 (1.1)		2.5[2.03,2.97]



Analysis 1.6. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 6 Erythrocytes.

Study or subgroup	Cordyceps N	Cordyceps Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sun 2004a	57	4.6 (0.8)	64	3.6 (0.6)		1[0.75,1.25]



Analysis 1.7. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 7 AST.

Study or subgroup	Cordyceps N	Cordyceps Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sun 2004a	57	34.7 (12.1)	64	52.3 (18.5)		-17.6[-23.11,-12.09]

Analysis 1.8. Comparison 1 *Cordyceps sinensis* versus azathioprine, Outcome 8 ALT.

Study or subgroup	Cordyceps N	Cordyceps Mean(SD)	AZA N	AZA Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sun 2004a	57	31.5 (11.4)	64	46.8 (17.5)		-15.3[-20.51,-10.09]

Comparison 2. *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Graft survival	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Serum creatinine	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Whole blood trough CsA concentration	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 3 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Pulmonary infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Nephrotoxicity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 AST	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 ALT	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 Albumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11 Uric acid	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 1 All-cause mortality.

Study or subgroup	Cordyceps+low dose CsA n/N	Standard dose CsA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ding 2011	2/83	4/99		0.6[0.11,3.17]
		Less with Cord+low dose	0.05 0.2 1 5 20	Less with std dose CsA

Analysis 2.2. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 2 Graft survival.

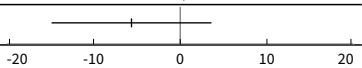
Study or subgroup	Cordyceps+low dose CsA n/N	Standard dose CsA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ding 2011	4/83	6/99		0.8[0.23,2.72]
		More with std dose CsA	0.1 0.2 0.5 1 2 5 10	More with Cord+low dose

Analysis 2.3. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 3 Acute rejection.

Study or subgroup	Cordyceps+low dose CsA n/N	Standard dose CsA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ding 2011	10/83	15/99		0.8[0.38,1.68]
		Less with Cord+low dose	0.1 0.2 0.5 1 2 5 10	Less with std dose CsA

Analysis 2.4. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 4 Serum creatinine.

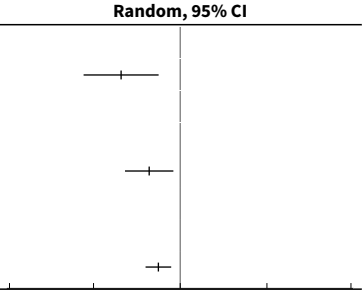
Study or subgroup	Cordyceps+low dose CsA		Standard dose CsA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Ding 2011	58	108.5 (26.6)	51	114.2 (22.5)		-5.62[-14.84,3.6]



Lower with Cord+low dose | Lower with std dose CsA

Analysis 2.5. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 5 Whole blood trough CsA concentration.

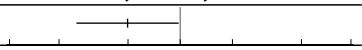
Study or subgroup	Cordyceps+low dose CsA		Standard dose CsA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
2.5.1 3 months						
Ding 2011	58	213.4 (57.5)	51	247.5 (57.5)		-34.1[-55.73,-12.47]
2.5.2 6 months						
Ding 2011	58	146.5 (28.7)	51	164.4 (43.1)		-17.9[-31.85,-3.95]
2.5.3 12 months						
Ding 2011	58	98.8 (14.4)	51	111.4 (23.3)		-12.6[-19.99,-5.21]



Lower with Cord+low dose | Lower with std dose CsA

Analysis 2.6. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 6 Pulmonary infection.

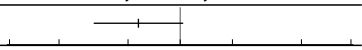
Study or subgroup	Cordyceps+low dose CsA	Standard dose CsA	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Ding 2011	10/83	24/99		0.5[0.25,0.98]



Less with Cord+low dose | Less with std dose CsA

Analysis 2.7. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 7 Nephrotoxicity.

Study or subgroup	Cordyceps+low dose CsA	Standard dose CsA	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Ding 2011	13/83	27/99		0.57[0.32,1.04]



Less with Cord+low dose | Less with std dose CsA

Analysis 2.8. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 8 AST.

Study or subgroup	Cordyceps+low dose CsA		Standard dose CsA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Ding 2011	69	34.5 (10.7)	67	40.2 (14.3)		-5.7[-9.95,-1.45]

Lower with Cord+low dose | -10 | -5 | 0 | 5 | 10 | Lower with std dose CsA

Analysis 2.9. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 9 ALT.

Study or subgroup	Cordyceps+low dose CsA		Standard dose CsA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Ding 2011	69	30.5 (10.1)	67	34.3 (12.5)		-3.8[-7.63,0.03]

Lower with Cord+low dose | -10 | -5 | 0 | 5 | 10 | Lower with std dose CSA

Analysis 2.10. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 10 Albumin.

Study or subgroup	Cordyceps+low dose CsA		Standard dose CsA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Ding 2011	69	43.2 (13.4)	67	37.7 (13.1)		5.5[1.05,9.95]

Higher with low dose CsA | -10 | -5 | 0 | 5 | 10 | Higher with Cord+low dose

Analysis 2.11. Comparison 2 *Cordyceps sinensis* plus low dose cyclosporin A versus standard dose cyclosporin A, Outcome 11 Uric acid.

Study or subgroup	Cordyceps+low dose CsA		Standard dose CsA		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Ding 2011	83	313.6 (99.2)	99	397.8 (132.2)		-84.19[-117.86,-50.52]

Lower with Cord+low dose | -200 | -100 | 0 | 100 | 200 | Lower with std dose CsA

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Cordyceps, this term only 2. (cordyceps sinensis*) in Clinical Trials 3. (Ophiocordyceps sinensis*) in Clinical Trials 4. (cordyceps*) in Clinical Trials 5. (dongchongxiacao) or (dong chong xia cao) or (dongchong xiacao) in Clinical Trials

(Continued)

	6. (chongcao*) or chong cao* in Clinical Trials 7. (1 OR 2 OR 3 OR 4 OR 5 OR 6) 8. MeSH descriptor Kidney Transplantation, this term only 9. (7 AND 8)
MEDLINE	1. Cordyceps/ 2. cordyceps sinensis.tw. 3. Ophiocordyceps sinensis.tw 4. cordyceps.tw. 5. (dongchongxiacao or dong chong xia cao).tw. 6. (chongcao or chong cao).tw. 7. or/1-6 8. Kidney Transplantation/ 9. and/7-8
EMBASE	1. Cordyceps Sinensis Extract/ 2. Cordyceps/ 3. cordyceps sinensis.tw. 4. Ophiocordyceps sinensis.tw 5. (dongchongxiacao or dong chong xia cao).tw. 6. (Chongcao or chong cao).tw. 7. or/1-6 8. exp kidney transplantation/ 9. and/7-8

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

(Continued)

	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias	*Low risk of bias:* The study appears to be free of other sources of bias.

(Continued)

Bias due to problems not covered elsewhere in the table	*High risk of bias:* Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: TH
2. Study selection: TH, MZ
3. Extract data from studies: TH, MZ
4. Enter data into RevMan: TH
5. Carry out the analysis: TH
6. Interpret the analysis: TH
7. Draft the final review: TH, JF
8. Disagreement resolution: JF
9. Update the review: TH

DECLARATIONS OF INTEREST

- Tao Hong: none known
- Minghua Zhang: none known
- Junming Fan: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the protocol and review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cordyceps; *Kidney Transplantation [mortality]; Adjuvants, Immunologic [*therapeutic use]; Azathioprine [therapeutic use]; Cyclosporine [therapeutic use]; Drugs, Chinese Herbal [*therapeutic use]; Graft Rejection [*prevention & control]; Graft Survival [*drug effects]; Immunosuppressive Agents [*therapeutic use]; Medicine, Chinese Traditional; Randomized Controlled Trials as Topic

MeSH check words

Humans